Stability Analysis of Transmission Dynamics of Tuberculosis with Multi-Drug Resistant and Mitigating Measures

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Abstract:
Based on the 2024 report from the World Health Organization, tuberculosis continues to pose a global threat. In response to this, we developed a modified five-compartmental SVIMDR model to evaluate the stability of the disease, specifically considering multi-drug-resistant patients, within a feasible human population. The stability analysis was conducted in relation to the reproduction number (R0) using the generalized Hyers Ulam stability, Jacobi method and modified Lyapunov-Volterra stability. The model was validated qualitatively using a modified Banach fixed point theorem and Lipchitz contraction condition approach. To assess the impact of multi-drug resistance on the infection dynamics, two relapse rates were incorporated to check the effect on the model which negatively impacts it. The model was estimated numerically using a modified Adam's Bashforth predictor-corrector method. The graphical solutions revealed that the introduced inhibitory effect (saturation factor) within the model demonstrated that as saturation increases, the infection become more stable (R0<1). According to the findings in this research, we will have fewer multi-drug-resistant patients provided the saturation factor is implemented properly.

Keywords: **Stability; Infection; Lyapunov-Volterra; Adams Bashforth; Saturation Factor.**

1. Introduction

MYCOBACTERIUM tuberculosis (Mtb) is the primary cause of tuberculosis (TB), a lung infection that continues to pose a serious threat to world health [1]. Although Mtb mostly affects the lungs, it can spread through the circulation to other organs, leading to extra pulmonary TB, which is often not communicable [2]. The symptoms of active tuberculosis, which include, night sweat fever, persistent coughing, weight loss, chest discomfort which are being spread by airborne droplets released by infected or contagious people. Although a skin diagnosis can identify an infection up to 4 weeks after contact, symptoms frequently take time to manifest [3]. Most people who become infected get latent tuberculosis, which has a 10% lifespan chance of developing into persistent TB [4, 5]. When the immune system is weakened, the bacteria that cause latent tuberculosis might reawaken after the latency period and develop to active TB. The likelihood of latent TB reactivation is greatly increased by the HIV virus co-infection [6].

Roughly 30% of people worldwide are infected with hidden tuberculosis (TB), which causes approximately 9 million fresh active infections and 2 million deaths annually, mostly in developing countries. [7]. Long-term antibiotic therapy is necessary for persistent TB to lower the chance of revival, albeit a cure is not certain. Patients with active TB who do not receive treatment have a death rate of more than 50%. Untreated TB in pregnant women can result in low birth weight and, in rare cases, congenital TB. Initial tuberculosis medications were not known to affect fetuses, even if they penetrate the placenta [8]. Treatment attempts have been hampered by the advent of drug-resistant Tuberculosis strains. For around ten to fifteen years, the Bacille Calmette Guérin (BCG) vaccination provides transient protection [9, 10]. It is crucial to have a thorough understanding of tuberculosis, including its genetic composition and mode of transmission. The potential of TB eradication was first raised by the discovery of medicines like isoniazid and streptomycin. But the HIV/AIDS pandemic and the rise of treatment resistance have stepped up international efforts to fight this chronic illness, especially in underdeveloped areas [1].

The requirement for strong modeling techniques to evaluate the effects of possible intervention options is highlighted by the intricate and diverse nature of infectious disease transmission at the population level [11]. A vital tool for comprehending the dynamics of tuberculosis transmission and assessing control strategies is mathematical modeling. Numerous modeling frameworks, such as compartmental, integer time series, and epidemiological models, have been investigated in earlier research. Even though this research provides light on latent infections and the effects of public health initiatives, more complex models that integrate data-driven methodologies and different control techniques are still required to guide successful responses for public health. [12–15]. The validation and improvement of mathematical models for infectious illnesses have been greatly aided by empirical data from a variety of populations and nations. Important

information on TB frequency, transmission patterns and incident rate, across geographical areas has been made possible by epidemiological research [16]. Comprehensive worldwide TB data has been gathered by the World Health Organization (WHO), providing important insights on the prevalence of the disease and the success of control initiatives [17]. Numerous infectious diseases have endemic patterns with yearly or multi-yearly fluctuations which are impacted by variables including weather, diseases of children, and school cycles. It is crucial to account for any seasonal fluctuations in pulmonary tuberculosis prevalence to fully represent the complexity of disease transmission [18]. There has been an informal effort to identify the best disease control techniques. Although spending money on early detection and therapy can lessen the impact of disease, there are several obstacles because of the wide range of possible approaches and unpredictable results [19].

2.0 Model formulation

To better understand the transmission dynamics of tuberculosis within a realistic human population, some assumptions were made. A modified SVIMDR compartmental deterministic model was developed, where S represents the susceptible class, V denotes the Vaccinated class, and it is assumed that newborns are vaccinated with (BCG) before reaching adulthood. However, over time the effectiveness of the vaccination diminishes. I stand for the infected class, MD refers to the Multi-Drug-Resistant individuals, and R represents the Recovered class. Additionally, the model incorporates an inhibitory effect known as the saturation coefficient (α), which reduces the severity of the infection. In this context, saturation refers to proper diagnosis and treatment of those infected with this infection, stability of the infection is achieved when the reproduction number less than unity (R0<1) which is the aim of this study. Moreover, two relapse rates were introduced into the model: representing relapse from initial treatment i.e. Reactivation of existing Mycobacterium tuberculosis and representing re-infection by Mycobacterium tuberculosis. These rates contributed to the creation of MD individuals.

The model formulation is represented in the schematic flow below.

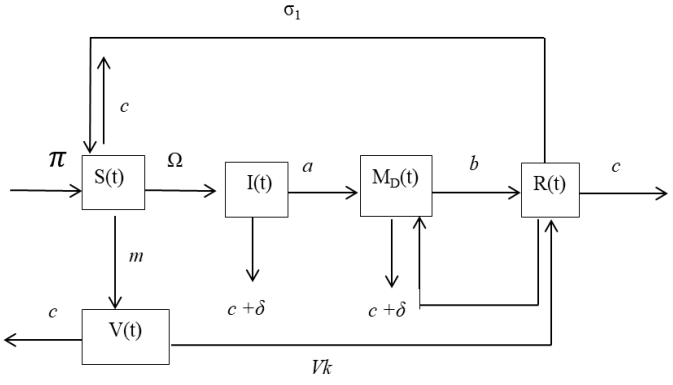

Figure 1: Schematic flow of the modified Tuberculosis model

2.1 The Tuberculosis model equation.

With the rate of change in each class of the model according to Figure 1 we have.

$$\left.\begin{aligned}
\frac{dS}{dt} &= \pi - ((\frac{\kappa I}{1+\alpha I}) + c + m)S + \sigma_1 R \\
\frac{dV}{dt} &= mS - (c+k)V \\
\frac{dI}{dt} &= (\frac{\kappa I}{1+\alpha I})S - (c+a+\delta)I \\
\frac{dM_D}{dt} &= aI - (c+\delta+b)M_D + \sigma_2 R \\
\frac{dR}{dt} &= bM_D - (c+\sigma_1+\sigma_2)R + Vk
\end{aligned}\right\} \quad (1)$$

For convenience we denote $\Omega = \frac{\kappa I}{1+\alpha I}$ which is the incident rate of the infection in this study.

Where the state variables have positive initial conditions

$$S(t) \geq 0, V(t) \geq 0, I(t) \geq 0, M_D(t) \geq 0 \quad (2)$$

3.0 Qualitative Analysis of the Model

3.1 Existence and Uniqueness of the Model Solution

To demonstrate the existence and uniqueness of the Tuberculosis model we employ the use of a modified Banach fixed point theorem.

Theorem 1. Let $\Upsilon = (M(L))^5$ be a Banach space and continuous on $L : M \to M$ equipped with the norm $(\|.\|)$ where the norm $(\|.\|)$ denote the supermum of the space $\Upsilon = (M(L))^5$ and similarly let $\Gamma_1 ... \Gamma_5$ be the kernels associated with the defined space. Then the Lipschitz contraction condition is satisfied if the kernels $\Gamma_1 ... \Gamma_5$ hold true for the inequality.

$0 \leq H_J < \infty$ where $j = 1...5$

Proof

The tuberculosis model equation (1) can alternatively be written as.

$$\left.\begin{aligned}
\Gamma_1(S,t) &= \pi - (\Omega + c + m)S + \sigma_1 R \\
\Gamma_2(V,t) &= mS - (c+k)V \\
\Gamma_3(I,t) &= \Omega S - (c+a+\delta)I \\
\Gamma_4(M_D,t) &= aI - (c+\delta+b)M_D + \sigma_2 R \\
\Gamma_5(R,t) &= bM_D - (c+\sigma_1+\sigma_2)R + Vk
\end{aligned}\right\} \quad (3)$$

Similarly let,

$$\left.\begin{aligned} U_1 &= \pi-(\Omega+c+m)S+\sigma_1 R \\ U_2 &= mS-(c+k)V \\ U_3 &= \Omega S-(c+a+\delta)I \\ U_4 &= aI-(c+\delta+b)M_D+\sigma_2 R \\ U_5 &= bM_D-(c+\sigma_1+\sigma_2)R+Vk \end{aligned}\right\} \quad (4)$$

Taking the partial derivative of (4) with respect to state variables we have.

$$H_1=\frac{\partial U_1}{\partial S}=-(\Omega+c+m)<\infty, H_2=\frac{\partial U_2}{\partial V}=-(c+k)<\infty, H_3=\frac{\partial U_3}{\partial I}=-(c+a+\delta)<\infty,$$
$$H_4=\frac{\partial U_4}{\partial S}=-(c+b+\delta)<\infty, H_5=\frac{\partial U_5}{\partial S}=-(c+\sigma_1+\sigma_2)<\infty$$

Let S_1,t and S_2,t be functions such that:

$$\begin{aligned} &\left\|\Gamma_1(S_1,t)-\Gamma_1(S_2,t)\right\|=\left\|-(\Omega+c+m)(S_1(t)-S_2(t))\right\|\le\left\|(\Omega+c+m)\right\|\left\|S_1(t)-S_2(t)\right\| \\ &\le(\Omega+c+m)\left\|S_1(t)-S_2(t)\right\|\le H_1\left\|S_1(t)-S_2(t)\right\| \end{aligned} \quad (5)$$

From (5) we can have:

$$\left\|\Gamma_1(S_1,t)-\Gamma_1(S_2,t)\right\|\le H_1\left\|S_1(t)-S_2(t)\right\|<\infty \quad (6)$$

From (6), Γ_1 Has satisfied the Lipschitz contraction condition since $(H_1...H_5)<\infty$ is the Lipschitz constant, hence it shows that the model equation of the susceptible class S (t) exists and stays unique.

Approaching the rest of the equations that make up of each class in this manner, we obtain.

$$\left.\begin{aligned} &\left\|\Gamma_2(V_1,t)-\Gamma_2(V_2,t)\right\|\le H_2\left\|V_1(t)-V_2(t)\right\|<\infty \\ &\left\|\Gamma_3(I_1,t)-\Gamma_3(I_2,t)\right\|\le H_3\left\|I_1(t)-I_2(t)\right\|<\infty \\ &\left\|\Gamma_4(M_{D1},t)-\Gamma_4(M_{D2},t)\right\|\le H_4\left\|M_{D1}(t)-M_{D2}(t)\right\|<\infty \\ &\left\|\Gamma_4(R_1,t)-\Gamma_4(R_2,t)\right\|\le H_5\left\|R_1(t)-R_2(t)\right\|<\infty \end{aligned}\right\} \quad (7)$$

Conclusively, we have been able to demonstrate that the system of equations (1) exists and remains unique.

3.2 Boundedness and Positivity of the model solution

Theorem 2: for all time t >0 the model remains bound and remains within limit.

Proof:

Let $\chi(t)$ represent the total population of the model, with this we have:

$$\chi(t)=S(t)+V(t)+I(t)+M_D(t)+R(t) \quad (8)$$

With respect to the rate of change in each class we obtain.

$$\chi'(t)=S'(t)+V'(t)+I'(t)+M'_D(t)+R'(t) \quad (9)$$

Simplifying (9) we obtain

$$\chi'(t)=\pi-(S(t)+V(t)+I(t)+M_D(t)+R(t)) \quad (10)$$

From (10) we have.

$$\chi'(t)=\pi-c(\chi) \quad (11)$$

Solving (11) we obtain.

$$\chi(t)\le\frac{\pi}{c} \quad (12)$$

Which indicates that the model can be found in the feasible region,

$$\Psi=[(S(t)+V(t)+I(t)+M_D(t)+R(t)\in R_+^5:\chi(t)\le\frac{\pi}{c})] \quad (13)$$

Additionally let $[(S(t),V(t),I(t),M_D(t),R(t)]$ Be positive and remain within limit, then there exists positive constant $(T_1...T_5)>0$, such that:

$$\left\|S(t)\right\|\le T_1,\left\|V(t)\right\|\le T_2,\left\|I(t)\right\|\le T_3,\left\|M_D(t)\right\|\le T_4,\left\|R(t)\right\|\le T_5 \quad (14)$$

Therefore, the solution set of the tuberculosis model (1) remains bound and stays within limit.

3.2.1 Positivity of the model solution

Theorem 3: for all time t>0 the tuberculosis model (1) equipped with positive initial conditions will remain positive and stay non-negative

Proof

From the first equation of the systems of equations (1) we have:

$\frac{dS}{dt}=\pi-(\Omega+c+m)S+\sigma_1 R$ Considering the parameters that include the susceptible class, the equation can alternatively be given as $\frac{dS}{dt}=-(\Omega+c+m)S$, obtaining the integrating factor from the last equation we have,

I.F $e^{\int-(\Omega+c+m)dt}=e^{-(\Omega+m+c)t}$ simplifying further we obtain,

$\int \frac{dS}{dt} e^{-(\Omega+c+m)t} \geq \int 0 = S(t)e^{-(\Omega+c+m)t} \geq A$, where A is the constant of integration,

Thus we have $S(t) \geq Ae^{(\Omega+c+m)t}$ as $t \to 0$, $S(t) \geq 0$,

conveying positivity in the susceptible class S(t). With this we can conclude that all other classes that made up the model will remain positive all-time t >0. i.e.

$V(t) \geq 0, I(t) \geq 0, M_D(t) \geq 0$ and $R(t) \geq 0$. (15)

3.3 Equilibrium Points

Equilibrium points are the stable state solution where the system is either immune to the disease (Infection free Points) or the persistence of the disease within the system (Endemic Point).

We will be considering the infection free point only which is the aim of this study

Solving the system of equation (1) with respect to infection free points we obtain.

$$P^0 = (S^0, V^0, I^0, M_D^0, R^0) = (\frac{\pi}{c}, 0, 0, 0, 0) \quad (16)$$

3.4 Basic Reproduction Number

The R_0 of the model will be computed using next generation matrix technique [20]. Using

$R_0 = \Delta(Y Z^{-1})$, where Y and Z is the Matrix of new infection and matrix of secondary infection respectively and Δ denote the maximum absolute value of the matrix $(Y Z^{-1})$.

This number is crucial in the dynamics of infectious diseases, it allows us to determine the rate at which the infection reproduces within the community, in other words it is the average rate of infection in the vulnerable group caused by other transfer infection. Additionally, this will guide in creating a proper control plan by focusing on some parameters that made up the reproduction number.

From the system of equation (1) we have.

$Y_1 = \Psi S$, recall that $\Omega = \frac{\kappa I}{1+\alpha I}$, here $\alpha = 0$,

hence $Y_1 = \kappa I S$, $Y_2 = 0$

Making use of the infected and multi-drug-resistant compartment because it is assumed that the infection is dominant in these set of people according to the proposed model with that, we obtain.

$$Y = \begin{bmatrix} \frac{\partial Y_1}{\partial I} & \frac{\partial Y_1}{\partial M_D} \\ \frac{\partial Y_2}{\partial I} & \frac{\partial Y_2}{\partial M_D} \end{bmatrix} = \begin{bmatrix} 0 & \kappa S \\ 0 & 0 \end{bmatrix} \quad (17)$$

For the secondary infection we also obtain.

$$Z_1 = -(c+a+\delta)I,$$

$$Z_2 = aI - (c+\delta+b)M_D + \sigma_2 R$$

$$Z = \begin{bmatrix} \frac{\partial Z_1}{\partial I} & \frac{\partial Z_1}{\partial M_D} \\ \frac{\partial Z_2}{\partial I} & \frac{\partial Z_2}{\partial M_D} \end{bmatrix} = \begin{bmatrix} -(c+a+\delta) & 0 \\ a & -(c+\delta+b) \end{bmatrix} \quad (18)$$

Using $R_0 = \Delta(Y Z^{-1})$ and at infection free we obtain.

$$R_0 = \frac{\kappa \pi a}{c(c+a+\delta)(c+b+\delta)}$$

3.5 Stability Analysis of the Tuberculosis model solution

3.5.1Local Stability Analysis

Definition 1: The stability analysis of this model will be conducted with respect to the reproduction number (R_0) and at infection free, which is one of the aims of this study, using the Jacobi method we will initially test for the local asymptotic stability of the model.

Theorem 4: if $R_0 < 1$ then model (1) is stable locally

Proof

With respect to the Reproduction number (R_0) the stability of the model will be checked using the infection free points

$$P^0 = (S^0, V^0, I^0, M_D^0, R^0) = (\frac{\pi}{c}, 0, 0, 0, 0)$$

The Jacobi function to be used is defined as:

$$J_0(S, V, I, M_D, R)$$

Let

$$\left.\begin{aligned} W_1 &= \pi - (\Omega+c+m)S + \sigma_1 R \\ W_2 &= mS - (c+k)V \\ W_3 &= \Omega S - (c+a+\delta)I \\ W_4 &= aI - (c+\delta+b)M_D + \sigma_2 R \\ W_5 &= bM_D - (c+\sigma_1+\sigma_2)R + Vk \end{aligned}\right\} \quad (19)$$

Taking the partial derivative of (19) with respect to each class we obtain.

$$J_0 = \begin{bmatrix} J_{11} & J_{12} & J_{13} & J_{14} & J_{15} \\ J_{21} & J_{22} & J_{23} & J_{24} & J_{25} \\ J_{31} & J_{32} & J_{33} & J_{34} & J_{35} \\ J_{41} & J_{42} & J_{43} & J_{44} & J_{45} \\ J_{51} & J_{52} & J_{53} & J_{54} & J_{55} \end{bmatrix} \quad (20)$$

Where:

$$J_{11} = -c, J_{12} = 0, J_{13} = 0, J_{14} = \kappa S, J_{15} = \sigma_1, J_{21} = 0, J_{22} = -(c+k), J_{23} = 0, J_{24} = 0, J_{25} = 0,$$

$$J_{31}=0, J_{32}=0, J_{33}=-(c+b+\delta-\frac{a\kappa S}{(c+a+\delta)}), J_{34}=\kappa S, J_{35}=0, J_{41}=0, J_{42}=0, J_{43}=0,$$
$$J_{44}=-(c+\delta+b), J_{45}=\sigma_2, J_{51}=0, J_{52}=k, J_{53}=0, J_{54}=0, J_{55}=-(c+\sigma_1+\sigma_2) \quad (21)$$

From the diagonal entries of (20) we have:

$J_{11}, J_{22}, J_{33}, J_{44}$ And J_{55} which are all negative (stable) according to local asymptotic stability rule,

However, it is a necessary condition that the Reproduction number must be less than unity (1) i.e. (R_0<1) for stability of the model (1) to hold at infection free points, hence from

$J_{33}=-(c+b+\delta-\frac{a\kappa S}{(c+a+\delta)})$ it can be rewritten as

$$J_{33}=-(c+b+\delta)(1-\frac{a\kappa S}{(c+b+\delta)(c+a+\delta)}) \le (1-R_0)(c+b+\delta) \quad (22)$$

From the inequality in (22), it is sufficient to conclude that $R_0<1$.

This indicates that if proper management of the infection is given priority within the community, the rate at which the infection will reproduce within the broader community will be minimized, even if one infectious individual is thrown into the population outbreak will not occur.

3.5.2Global Stability

In this section we want to further investigate the stability of the tuberculosis model (1) in a larger region (Global) by employing the use of modified Lyapunov-Volterra method as follows.

Let the Lyapunov function be defined as:

$$H=g_1(S-S^*)^2+g_2(V-V^*)^2+g_3(I-I^*)^2+g_4(M_D-M_D{}^*)^2+g_5(R-R^*)^2 \quad (23)$$

Where $(g_1...g_5)>0$ Are positive weight Functions

Differentiating (23) along the solution path of system of equations (1) we obtain:

$$\frac{dH}{dt}=2g_1(S-S^*)\frac{dS}{dt}+2g_2(V-V^*)\frac{dV}{dt}+2g_3(I-I^*)\frac{dI}{dt}$$
$$+2g_4(M_D-M_D{}^*)\frac{dM_D}{dt}+2g_5(R-R^*)\frac{dR}{dt} \quad (24)$$

Substituting the model (1) in (24) we obtain:

$$\frac{dH}{dt}=2g_1(S-S^*)[\pi-(\Omega+c+m)S+\sigma_1R]+2g_2(V-V^*)$$
$$[mS-(c+k)V]+2g_3(I-I^*)[\Omega S-(c+a+\delta)I]$$
$$+2g_4(M_D-M_D{}^*)[aI-(c+\delta+b)M_D+\sigma_2R]$$
$$++2g_4(R-R^*)[bM_D-(c+\sigma_1+\sigma_2)R+Vk] \quad (25)$$

At Tuberculosis infection free we have:

$$\Upsilon=[S(t)-S^*(t), V(t)-V^*(t), I(t)-I^*(t), M(t)-M_D{}^*(t), R(t)-R^*(t)]=diag(g_1,g_2,g_3,g_4,g_5)$$

This is associated with the matrix:

$$L=\begin{bmatrix} -(\Omega+c+m) & 0 & \frac{\kappa S}{1+\alpha I} & 0 & \sigma_1 \\ m & -(c+k) & 0 & 0 & 0 \\ \Omega & 0 & -(c+a+\delta) & 0 & 0 \\ 0 & 0 & a & -(c+\delta+b) & \sigma_2 \\ 0 & k & 0 & b & -(c+\sigma_1+\sigma_2) \end{bmatrix} \quad (26)$$

To properly establish the global stability of the tuberculosis model (1), the matrix L defined by (26) is Lyapunov-Voltrerra stable if and only if the following conditions is satisfied [23]

(F_1) the eigen-valued of L are all negative (stable) real negative part if there exist a matrix $N>0$ such that $NL+N^TL^T<0$ where N is a positive definite symmetric

(F_2) the Matrix L which is nonsingular is Lyapunov-Volterra stable if there exist a diagonal $R_{n\times n}$ matrix which is positive such that $RL+L^TR^T<0$

(F_3) $F=\begin{bmatrix} F_{11} & F_{12} \\ F_{21} & F_{22} \end{bmatrix}$ is Lyapunov-Volterra stable if $F_{11}<0$, $F_{22}<0$ and determinant $(F_{11}F_{22}-F_{12}F_{21})>0$

Theorem 5: the system (26) that defines the Matrix L is Lyapunov-Volterra stable

Proof

Let F = L be a 3 x 3 matrix gotten from (26) by deleting it 4th and 5th rows and Columns respectively, we obtain:

$$F=L=\begin{bmatrix} -(\Omega+c+m) & 0 & \frac{\kappa S}{1+\alpha I} \\ m & -(c+k) & 0 \\ \Omega & 0 & -(c+a+\delta) \end{bmatrix} \quad (27)$$

Considering (F_1- F_3) we provide proof to establish that $F^{-1}=L^{-1}$ is stable diagonally, hence with this it is sufficient to say matrix L is Lyapunov-Volterra stable at infection free of the Tuberculosis model (1).

Lemma 1: the system (27) is stable diagonally

Proof

To establish the diagonal stability of F, clearly (i) $F_{33}<0$ (ii) considering (F_3) we will establish that matrix F is diagonally stable

From (27) we obtain

$$F = \begin{bmatrix} -(\Omega + c + m) & 0 \\ m & -(c+k) \end{bmatrix} \quad (28)$$

Clearly From (28) $F_{11}<0$, $F_{22}<0$ and similarly det(F) > 0 i.e. $|(\Omega + c + m)(c+k)| > 0$ hence F is stable diagonally.

Next is to establish that F^{-1} is stable diagonally

Let $F = \begin{bmatrix} F_{11} & F_{12} \\ F_{21} & F_{22} \end{bmatrix}$ then

$$F^{-1} = \frac{Adj(F)}{|F|} = \begin{bmatrix} -\frac{1}{(\Omega + c + m)} & 0 \\ \frac{m}{(c+k)(c+m+\Omega)} & -\frac{1}{(c+k)} \end{bmatrix} \quad (29)$$

Clearly from (29) $F_{11}^{-1} < 0$ and $F_{22}^{-1} < 0$ hence $F^{-1}$is stable diagonally since its determinant $|F^{-1}| = \left|(\frac{1}{(\Omega + c + m)})(\frac{1}{(c+k)})\right| > 0$.

From (29) it is sufficient to conclude that $F^{-1} = L^{-1}$ is diagonally stable

Therefore, the matrix L Is Lyapunov-Volterra stable at infection free

This completes the proof.

3.5.3Generalized Hyers Ulam Stability Analysis

Additionally, to further validate the stability of tuberculosis model (1), we apply the generalized Hyers Ulam stability analysis for differential equation.

According to Hyers Ulam the tuberculosis model (1) can be given in the form

$E(t) = P(t, E(t)), E(0) = E_0 \geq 0$ With $t_0 \leq t \leq T$ where $T < \infty$ (30)

Here

$P(t, E(t)), = [E_1(S(t), t), E_2(V(t), t), E_3(I(t), t), E_4(M_D(t), t), E_5(R(t), t)]$

Where:

$$E_1 = \frac{dS}{dt}, E_2 = \frac{dV}{dt}, E_3 = \frac{dI}{dt}, E_4 = \frac{dM_D}{dt}, E_5 = \frac{dR}{dt}$$

Theorem 5: let $J : N \times E \to E$ be a function that is continuously differentiable and also fulfills the Lipschitz condition $|J(t, S_{11}...S_{1n}) - t, (S_{21}...S_{2n})| \leq Y$ where Y is the Lipschitz constant, then the tuberculosis model (1) possess the generalized Hyers Ulam Stability constant $\frac{YQ}{1-YQ}$ such that

$|S_{11}(t) - S_{12}(t)| \leq \frac{YQ}{1-YQ}$ Where $Q > 0$ with $0 < YQ < 1$

Proof

Let Y be a constant which is positive with $YQ < 1$

Let $S_{11}(t) \in E_1$, where $S_{11}(t)$ is a unique solution of model (1) with positive initial condition, such that $S_{11}(t) = S_{12}(t)$; Where $S_{12}(t) \in E_1$ and for every $\varepsilon > 0$ we obtain;

$$|S_{11}(t) - S_{12}(t)| \leq \frac{YQ}{1-YQ}\varepsilon \quad (31)$$

Using the same approach, we will establish the generalized Hyers Ulam stability for other classes that are made of the tuberculosis model (1) in doing so we obtain:

$$\left.\begin{aligned} |V_{11}(t) - V_{12}(t)| &\leq \frac{YQ}{1-YQ}\varepsilon \\ |I_{11}(t) - I_{12}(t)| &\leq \frac{YQ}{1-YQ}\varepsilon \\ |M_{D11}(t) - M_{D12}(t)| &\leq \frac{YQ}{1-YQ}\varepsilon \\ |R_{11}(t) - R_{12}(t)| &\leq \frac{YQ}{1-YQ}\varepsilon \end{aligned}\right\} \quad (32)$$

Conclusively, it is sufficient to conclude that the modified tuberculosis model (1) will continue to be stable ($R_0<1$) analytically for all time t > 0

This completes the proof.

3.5.4Numerical solution

The set of differential equations used will be estimated using Adams Bashforth Predictor-corrector method to obtain numerical (Approximate) values. The algorithm to the method will be given below.

Recall that the classical Runge-Kutta 4th Order numerical Scheme will be needed as the starting point/initial point before the Adams Bashforth method will be implemented

The Runge-Kutta 4th Order is given as:

$x_{n+1} = x_n + \frac{1}{6}(k_1 + 2k_2 + 3k_3 + k_4)$, where:

$n = 1, 2, 3...N$ and N is the number of grid Point.

The predictor:

$$x_{n+1} = x_n + \frac{b}{24}(55y_n - 59y_{n-1} + 37y_{n-2} - 9y_{n-3}) \quad (33)$$

The corrector:

$$x_{n+1}^{(k)} = x_n^{(k)} + \frac{b}{24}(9y_{n+1}^{(k)} + 19y_n^{(k)} - 5y_{n-1}^{(k)} + y_{n-2}^{(k)}) \quad (34)$$

Where *b* is the step size, *k= 0,1,2…,* the local truncation errors for both predictor and corrector is given by

$$D_n = \frac{251}{720}b^5x^5(\chi) \text{ and } D_n^{(k)} = \frac{251}{720}b^5x^5(\chi)$$

Implementing the numerical scheme defined above we have.

The predictor.

$$\left.\begin{aligned}
S_{n+1} &= S_n + \frac{b}{24}(55(S_n) - 59(S_{n-1}) + 37(S_{n-2}) - 9(S_{n-3})) + D_n \\
V_{n+1} &= V_n + \frac{b}{24}(55(V_n) - 59(V_{n-1}) + 37(V_{n-2}) - 9(V_{n-3})) + D_n \\
E_{n+1} &= E_n + \frac{b}{24}(55(E_n) - 59(E_{n-1}) + 37(E_{n-2}) - 9(E_{n-3})) + D_n \\
I_{n+1} &= I_n + \frac{b}{24}(55(I_n) - 59(I_{n-1}) + 37(I_{n-2}) - 9(I_{n-3})) + D_n \\
R_{n+1} &= R_n + \frac{b}{24}(55(R_n) - 59(R_{n-1}) + 37(R_{n-2}) - 9(R_{n-3})) + D_n
\end{aligned}\right\} \quad (35)$$

The corrector:

$$\left.\begin{aligned}
S_{n+1}^{(k)} &= \frac{b}{24}(9(S_{n+1}^{(k)}) + 19(S_n^{(k)}) - 5(V_{n-1}^{(k)}) + S_{n-2}^{(k)}) + D_n^{(k)} \\
V_{n+1}^{(k)} &= \frac{b}{24}(9(V_{n+1}^{(k)}) + 19(V_n^{(k)}) - 5(V_{n-1}^{(k)}) + V_{n-2}^{(k)}) + D_n^{(k)} \\
E_{n+1}^{(k)} &= \frac{b}{24}(9(E_{n+1}^{(k)}) + 19(E_n^{(k)}) - 5(E_{n-1}^{(k)}) + E_{n-2}^{(k)}) + D_n^{(k)} \\
I_{n+1}^{(k)} &= \frac{b}{24}(9(I_{n+1}^{(k)}) + 19(I_n^{(k)}) - 5(I_{n-1}^{(k)}) + I_{n-2}^{(k)}) + D_n^{(k)} \\
R_{n+1}^{(k)} &= \frac{b}{24}(9(R_{n+1}^{(k)}) + 19(R_n^{(k)}) - 5(R_{n-1}^{(k)}) + R_{n-2}^{(k)}) + D_n^{(k)}
\end{aligned}\right\} \quad (36)$$

4.0 Numerical Simulations

In this section numerical simulation was carried out using MATLAB software to check the overall dynamics of tuberculosis model and to numerically check the impact of various parameters on the model. The Adams Bashforth Predictor-corrector technique has been inserted into the MATLAB numerical scheme to carry out these simulations.

According to the World health organization report of 2024 on tuberculosis case of Nigeria from 2000-2024, the incidence (per 100,000) is used as the initial conditions of our state variables as follows

$$S(t_0) = 467,000, V(t_0) = 150,000, I(t_0) = 125,000, M_D(t_0) = 2975, R(t_0) = 50 \quad (37)$$

The initial conditions and the parameter values given in Table 1 are used simultaneously for the simulations

4.1 Results and Discussions

The stability and Mathematical well-posed (accuracy) of the Tuberculosis model (1) with respect to the reproduction number less than unity (1) is demonstrated in Figure 2 representing the real-life situation and that the population co-exist within the model.

Figure 3 and 4 curves demonstrated how the increasing rate of "relapses" and re-infection impacted the population dynamics. It has been noted that a variety of factors may render a person who has recovered from the Tuberculosis infection become vulnerable, or even re-contact the infection after a year or two, for instance inadequate treatment from the initial infection can reactivate the M. tuberculosis within individual or reinfection after the initial treatment, these two often leads to Multi-drug resistance tuberculosis, with this there will be persistence of the infection within the community i.e. (R_0>1). Additionally, these two rates increase the numbers of vulnerable and infected individuals in these groups, necessary health care interventions are needed to flatten out this deadly disease in these groups.

TABLE 1
THE INITIAL CONDITIONS AND THE PARAMETER VALUES GIVEN

Parameters	Biological meaning	Values	Source
π	Rate of Birth	0.04	[24]
a	Rate of progression to multi-drug-resistant class from infected	0.0012	Assumed
δ	Disease induced death rate	0.003	[24]
κ	Infection rate	0.3	[24]
c	Natural death rate	0.0001914	[24]
α	Inhibitory effect (saturation co-efficient)	(0-1)	Fitted
b	Rate of progression to recover from multi-drug-resistant class	0.0250	Assumed
k	Rate of progression to recovered from vaccinated individual	0.009	Assumed
m	Vaccination rate	0.009	[24]
σ_1	Relapse rate from reactivation of existing *Mycobacterium tuberculosis*	(0-1)	Fitted
σ_2	Re-infection by *Mycobacterium tuberculosis*	(0-1)	Fitted

Health care professionals should encourage individuals that are currently being treated for tuberculosis infection to complete their treatment and awareness of how not to get re-infected to avoid being resistant to tuberculosis treatment infection which in turn leads to multi-drug-resistant group

According to Figure 5, the increasing rate of vaccination on the population density is highly recommended, with this, we recommend primary health care centers and hospitals to have a specialized center for tuberculosis cases; it is highly encouraged that all newly born babies are compulsorily given an improved tuberculosis vaccine at regular interval as prescribed by the health practitioners. With these the vaccinated class will instantaneously reach stability state. While the effectiveness of improved vaccines may lower the incidence of the infection, a sizable section of the population may still be at risk of infection, due to factors like declining immunity from the vaccine, the constant stream of new babies, and the possibility of vaccination escape variations. Additionally, despite enhanced vaccination, the community may still contain vulnerable individuals due to the usually long incubation periods of tuberculosis. However, if the infection is given priority by necessary health care professionals it can be reduced to bare minimum.

In Figures 6, 7 and 8 the effect of the saturation factor (α) that was embedded in the model was simulated to investigate its impact, saturation factor (α) in this context refers to Awareness based intervention (ABI), development of powerful vaccine, proper treatment of infectious individuals to avoid multi-drug resistant tuberculosis individuals in the community which will require a comprehensive and extensive treatment.

With the proper implementation of the saturation factor (α), these result in flattening out of the disease in the infected (Figure 6) and Multi-drug (Figure 7) resistance group and the attendant effect could be seen in the recovered individuals (Figure 8) which causes a significant rise in the recovered class with the increasing rate of the saturation factor (α). Which means these groups of individuals will gradually ease to infection Free State (stability). This is due to the Awareness Based Intervention efforts and the distribution of extremely effective vaccinations to primary and secondary health centers. Additionally, the number of people that will need treatment will decrease in tandem with the prevalence of active tuberculosis cases, which is reduced because of the mitigating techniques applied. Although fewer people starting treatment could at first imply a decline in recovery rates, the observed decline is more likely to be the result of fewer new cases.

The number of people that are done with treatment and moving into the recovered group inevitably declines over time as the infection incidence declines which in turn leads to stability within the broader community ($R_0 < 1$).

A comparative analysis was done numerically between the simulated data and the real data, which was shown in Figure 9, demonstrating the mathematical well posed of the proposed Model.

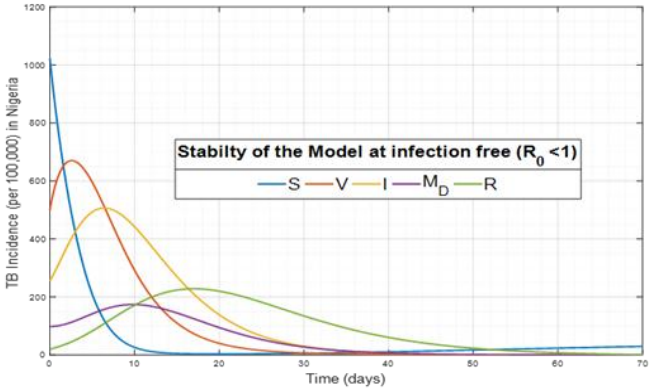

Figure 2: Transmission dynamics of the stability and Mathematical well-posed (accuracy) of the Tuberculosis model (1)

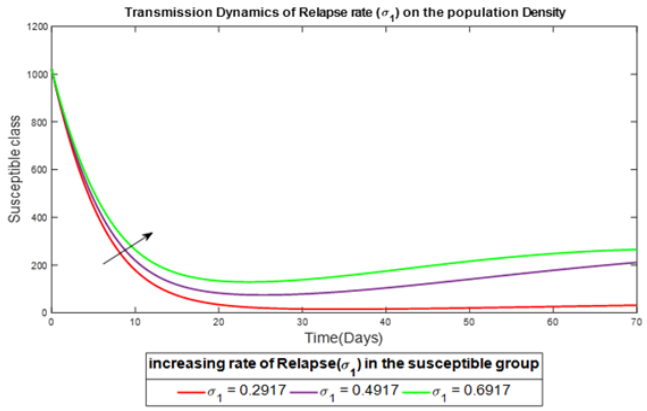

Figure 3: Transmission dynamics of relapse rate in the susceptible class.

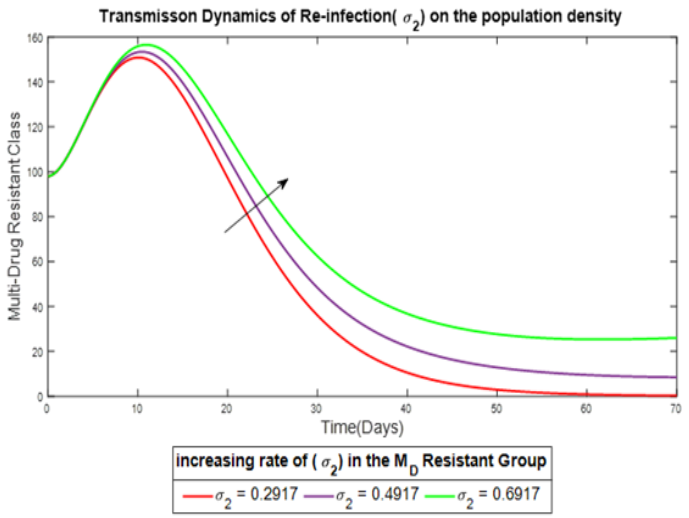

Figure 4: Transmission dynamics of re-infection rate in the multi-drug-resistant class.

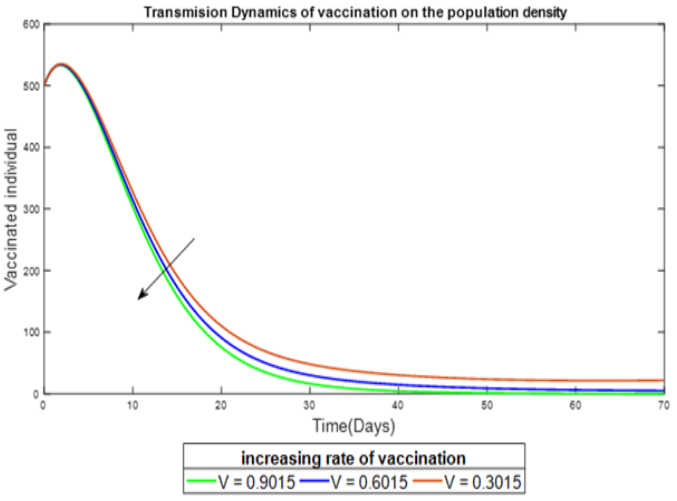

Figure 5: Transmission dynamics of vaccination rate in the vaccinated individual.

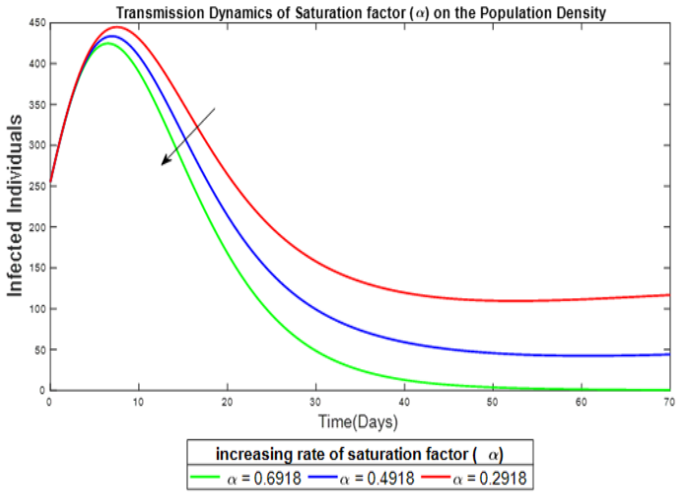

Figure 6: The effect of saturation factor (treatment) in the infected class.

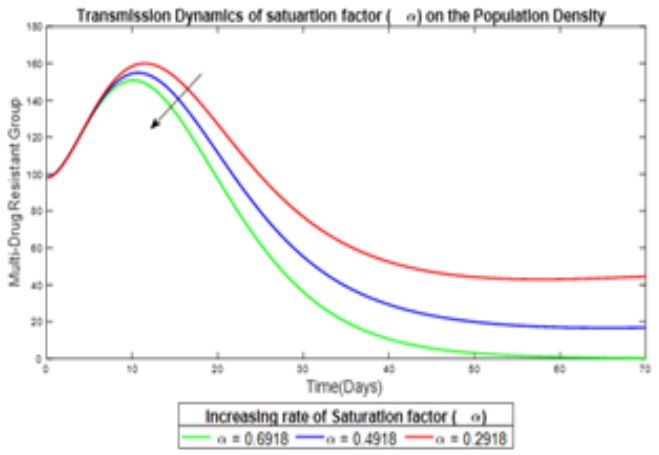

Figure 7: The effect of saturation factor (treatment) in the multi-drug resistant group.

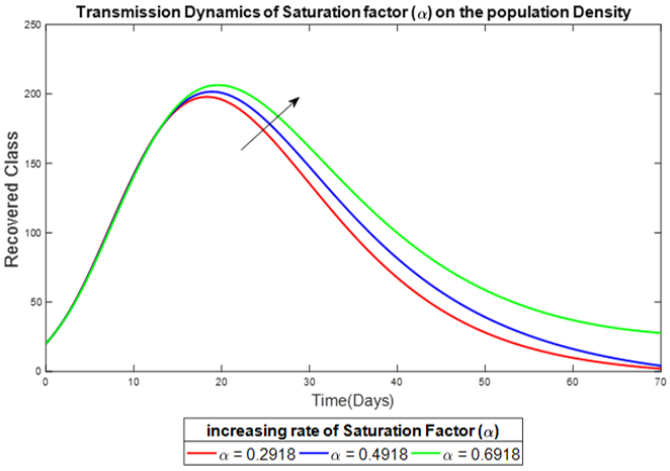

Figure 8: The effect of saturation factor (treatment) in the recovered class.

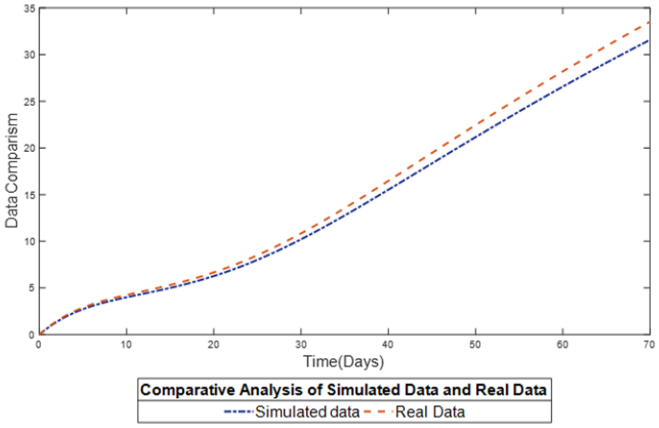

Figure 9: Comparative analysis of the reported data and the simulated (fitted) data.

CONCLUSION

Using a deterministic model, equipped with Ordinary differential equations, we have investigated the stability of the transmission dynamics of Tuberculosis with Multi-drug resistance individuals. By using a modified Banach Fixed-Point theorem, we demonstrated the uniqueness and existence of the model (1). Furthermore, we established the boundedness and positivity of the model within feasible regions. Moving forward, the stability was checked with respect to the reproduction number (R_0). The stability analysis was rigorously analyzed using Jacobi technique, modified Lyapunov-Volterra stability for matrices and the generalized Hyers Ulam stability for differential equations. The results proved to be correct analytically. The Adams Bashforth predictor-corrector approach was used to estimate the model numerically. Finally, the findings explain the effect of different parameters on the model impacting the model significantly; it is found that the present model's integration of saturation factor affects how quickly solution paths approach to steady state (infection free). These results add to the body of data supporting the idea that awareness-based intervention and proper treatment of infectious individual is highly recommended to flatten out disease in the broader community.

Conflict of interest

The authors have no conflict of interest to declare.

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